Notice of Allowability	Application No.	Applicant(s)	
	09/981,344	MIRKIN ET AL.	
	Examin r	Art Unit	
	Jezia Riley	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *Amdt filed 10/10/03*.
2. ☒ The allowed claim(s) is/are *1-22 and 433-444*.
3. ☐ The drawings filed on _____ are accepted by the Examiner.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.
5. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
   (a) ☐ The translation of the foreign language provisional application has been received.
6. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

7. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

8. ☒ CORRECTED DRAWINGS must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No. ____.
   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the Examiner.
   (c) ☒ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No. 11/03.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet.

9. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1☐ Notice of References Cited (PTO-892)
2☐ Notice of Informal Patent Application (PTO-152)
3☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
4☐ Interview Summary (PTO-413), Paper No.____ .
5☒ Information Disclosure Statements (PTO-1449), Paper No. ____.
6☐ Examiner's Amendment/Comment
7☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
8☐ Examiner's Statement of Reasons for Allowance
9☐ Other .

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

The formal drawings are required.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jezia Riley whose telephone number is 703-305-6855. The examiner can normally be reached on 9:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Friday, November 14, 2003

JEZIA RILEY
PRIMARY EXAMINER

ALLOWED CLAIMS/ TJ

1. (Currently amended) A method of detecting a nucleic acid having at least two portions, the method comprising:

providing a type of nanoparticles having oligonucleotides attached thereto, the oligonucleotides on each nanoparticle having a sequence complementary to the sequence of at least two portions of the nucleic acid;

contacting the nucleic acid and the nanoparticles under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles with the two or more portions of the nucleic acid to form a complex, the complex having a sharp melting profile and increased melting temperature relative to a melting profile and a melting temperature of an analogous complex formed with the nucleic acid and unlabeled or fluorophore-labeled oligonucleotides having a sequence identical to the oligonucleotides bound to the nanoparticles to allow for selective discrimination of any nucleotide insertion, deletion, or mismatch in the nucleic acid; and

observing a detectable change brought about by hybridization of the oligonucleotides on the nanoparticles with the nucleic acid.

2. (Currently amended) A method of detecting nucleic acid having at least two portions, the method comprising:

contacting the nucleic acid with at least two types of nanoparticles having oligonucleotides attached thereto, the oligonucleotides on the first type of nanoparticles having a sequence complementary to a first portion of the sequence of the nucleic acid, the oligonucleotides on the second type of nanoparticles having a sequence complementary to a second portion of the sequence of the nucleic acid, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles with the nucleic acid to form a complex, the complex having a sharp melting profile and increased melting temperature relative to a melting profile and a melting temperature of an analogous complex

formed with the nucleic acid and at least two types of unlabeled or fluorophore-labeled oligonucleotides, a first type and a second type of unlabeled or fluorophore-labeled oligonucleotides having sequences identical to the oligonucleotides bound to the first and second types of nanoparticles respectively to allow for selective discrimination of any nucleotide insertion, deletion, or mismatch in the nucleic acid; and

observing a detectable change brought about by hybridization of the oligonucleotides on the nanoparticles with the nucleic acid.

3. (Currently amended) The method according to any one of claims 1 or 2 [of Claim 2] wherein the contacting conditions include freezing and thawing.

4. (Currently amended) The method according to any one of claims 1 or 2 [of Claim 2]wherein the contacting conditions include heating.

5. (Currently amended) The method according to any one of claims 1 or 2 [of Claim 2]] wherein the detectable change is observed on a solid surface.

6. (Currently amended) The method according to any one of claims 1 or 2 [of Claim 2] wherein the detectable change is a color change observable with the naked eye.

7. (Currently amended) The method [of Claim] according to claim 6 wherein the color change is observed on a solid surface.

8. (Currently amended) The method according to any one of claims 1 or 2 [of Claim 2] wherein the nanoparticles are made of gold.

9. (Currently amended) The method [of Claim] according to claim 2 wherein the oligonucleotides attached to the nanoparticles are labeled on their ends not attached to the nanoparticles with molecules that produce a detectable change upon hybridization of the oligonucleotides on the nanoparticles with the nucleic acid.

10. (Currently amended) The method [of Claim] according to claim 9 wherein the nanoparticles are metallic or semiconductor nanoparticles and the oligonucleotides attached to the nanoparticles are labeled with fluorescent molecules.

11. (Currently amended) The method [of Claim] according to claim 2 wherein:

the nucleic acid has a third portion located between the first and second portions, and the sequences of the oligonucleotides on the nanoparticles do not include sequences complementary to this third portion of the nucleic acid; and

the nucleic acid is further contacted with a filler oligonucleotide having a sequence complementary to this third portion of the nucleic acid, the contacting taking place under conditions effective to allow hybridization of the filler oligonucleotide with the nucleic acid.

12. (Currently amended) The method according to any one of claims 1 or 2 [of Claim 2] wherein the nucleic acid is viral RNA or DNA.

13. (Currently amended) The method according to any one of claims 1 or 2 [of Claim 2] wherein the nucleic acid is a gene associated with a disease.

14. (Currently amended) The method according to any one of claims 1 or 2 [of Claim 2] wherein the nucleic acid is a bacterial DNA.

15. (Currently amended) The method according to any one of claims 1 or 2 [of Claim 2] wherein the nucleic acid is a fungal DNA.

16. (Currently amended) The method according to any one of claims 1 or 2 [of Claim 2]]wherein the nucleic acid is a synthetic DNA, a synthetic RNA, a structurally-modified natural or synthetic RNA, or a structurally-modified natural or synthetic DNA.

17. (Currently amended) The method according to any one of claims 1 or 2 [of Claim 2] wherein the nucleic acid is from a biological source.

18. (Currently amended) The method according to any one of claims 1 or 2 [of Claim 2] wherein the nucleic acid is a product of a polymerase chain reaction amplification.

19. (Currently amended) The method according to any one of claims 1 or 2 [of Claim 2] wherein the nucleic acid is contacted with the first and second types of nanoparticles simultaneously.

20. (Currently amended) The method according to any one of claims 1 or 2 [of Claim 2] wherein the nucleic acid is contacted and hybridized with the oligonucleotides on the first type of nanoparticles before being contacted with the second type of nanoparticles.

21. (Currently amended) The method [of Claim] according to claim 20 wherein the first type of nanoparticles is attached to a substrate.

22. (Currently amended) The method according to any one of claims 1 or 2 [of Claim 2] wherein the nucleic acid is double-stranded and hybridization with the oligonucleotides on the nanoparticles results in the production of a triple-stranded complex.

433. (Original) The method according to any one of claims 1 or 2, wherein the oligonucleotides are attached to the nanoparticles in a stepwise ageing process comprising (i) contacting the oligonucleotides with the nanoparticles in a first aqueous solution for a period of time sufficient to allow some of the oligonucleotides to bind to the nanoparticles; (ii) adding at least one salt to the aqueous solution to create a second aqueous solution; and (iii) contacting the oligonucleotides and nanoparticles in the second aqueous solution for an additional period of time to enable additional oligonucleotides to bind to the nanoparticles.

434. (Original) The method according to claim 433, wherein the salt solution has an ionic strength sufficient to overcome at least partially the electrostatic attraction or repulsion of the oligonucleotides for the nanoparticles and the electrostatic repulsion of the oligonucleotides for each other.

435. (Currently amended) The method [of Claim] according to claim 433 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

436. (Currently amended) The method [of Claim] according to claim 435 wherein the nanoparticles are gold nanoparticles.

437. (Currently amended) The method [of Claim] according to claim 436 wherein the oligonucleotides include a moiety comprising a functional group which can bind to a nanoparticle.

438. (Currently amended) The method [of Claim] according to claim 433 wherein all of the salt is added to the water in a single addition.

439. (Currently amended) The method [of Claim] according to claim 433 wherein the salt is added gradually over time.

440. (Currently amended) The method [of Claim] according to claim 433 wherein the salt is selected from the group consisting of sodium chloride, magnesium chloride, potassium chloride, ammonium chloride, sodium acetate, ammonium acetate, a combination of two or more of these salts, one of these salts in a phosphate buffer, and a combination of two or more these salts in a phosphate buffer.

442. (Currently amended) The method [of Claims] according to any one of claims 1 or 2 wherein the oligonucleotides present on surface of the nanoparticles at a surface density of at least 10 picomoles/cm^2.

443. (Currently amended) The method [of Claim] according to claim 442 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 15 picomoles/cm^2.

444. (Currently amended) The method [of Claim] according to claim 443 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of from about 15 picomoles/cm^2 to about 40 picomoles/cm^2.